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**Title page**

**Non-Pharmacological management of Orthostatic Hypotension in older people: A systematic review. The SENATOR ONTOP series**

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**Brief summary:** Our review revealed there is no strong evidence to recommend any non-pharmacological therapies for treating OH in older people, though lower limb and abdominal compression bandaging may help.

## 40 **Abstract**

### 41 **Objectives**

42 Non-pharmacological therapies are often recommended as a first line treatment for  
43 orthostatic hypotension (OH). However, the true effect of non-pharmacological therapy  
44 remains unclear, particularly in the older population. We undertook a systematic review  
45 evaluating the efficacy of non-pharmacological interventions in older people with OH to  
46 provide evidence-based recommendations.

### 47 **Design**

48 Systematic review of systematic reviews

### 49 **Setting and Participants**

50 MEDLINE, PubMed, EMBASE, and Cochrane Database of Systematic Reviews, CINHAL and  
51 PsychINFO were searched up to June 2018. Two reviewers identified eligible systematic  
52 reviews from which primary studies were selected. We included studies both randomized  
53 and non-randomized studies that evaluated any type of non-pharmacological intervention  
54 and reported outcomes of change in postural drop in systolic blood pressure (SBP) and/or  
55 orthostatic symptoms measured using any validated instrument. The Cochrane risk of bias  
56 tool was used, with recommendations based on the GRADE approach.

### 57 **Results**

58 Eleven trials were included. Meta-analysis of lower limb compression showed a reduction in  
59 the postural drop in SBP of 9.83 mmHg (95%CI -12.56, -7.11), whereas abdominal  
60 compression showed a larger reduction in postural drop in SBP of 12.30mmHg (95%CI -  
61 18.20, -6.39). Compression therapy was also beneficial in reducing OH symptoms. However,

62 the quality of the evidence for compression therapy was very poor. One study each was  
63 identified for sleeping-head-up (SHU), home based resistance training (HBRT) and multi-  
64 component intervention but did not significantly reduce postural SBP drop. Bolus water  
65 drinking was effective in one study but the study was of low quality.

## 66 **Conclusions/implications**

67 There is no high quality evidence to recommend any of the non-pharmacological therapies  
68 for the management of OH in older people. Yet, we make a weak recommendation for lower  
69 limb and abdominal compression therapy based on very low quality evidence. Large-scale  
70 trials are warranted in older people to substantiate the efficacy of non-pharmacological  
71 therapies in OH.

## Introduction

Orthostatic hypotension (OH) is extremely common in older people and increases with advancing age<sup>1</sup>. An International consensus statement defined OH as a sustained reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 minutes of standing or head-up tilt to at least 60° on a tilt table<sup>2</sup>. Prevalence of OH varies greatly, from 5% to 70% depending on the setting or population<sup>3,4</sup>. Saedon et al. reported that the pooled prevalence of OH was 22.2% and 23.9% in community dwelling older people and in long-term care settings respectively<sup>5</sup>. A cross-sectional cohort study involving 653 home-dwelling people aged 75 years and above reported an OH prevalence of 34%<sup>6</sup>. In addition to ageing, polypharmacy is also associated with increased prevalence of OH, being reported in up to 65% of veterans attending a geriatrics clinic<sup>7</sup>.

Medications that increase the risk of OH include vasodilators, antihypertensives,  $\beta$ -blockers, calcium antagonists, renin-angiotensin inhibitors,  $\alpha$ -blockers, dopaminergic agents, antipsychotics, antidepressants and sedative-hypnotics<sup>8-12</sup>. OH is significantly associated with coronary heart disease, heart failure, transient ischaemic attacks, isolated systolic hypertension, and carotid stenosis<sup>1,13-15</sup>. The annual rate of OH-related hospitalizations, from a nationwide inpatient sample in 2004 was 36 per 100,000 US adults which increased to 233 per 100,000 in patients aged 75 years or older. OH was the primary diagnosis in 35% of these hospitalizations<sup>16</sup>. Additionally, OH is an independent risk factor for falls<sup>1,17,18</sup> and all-cause mortality<sup>17,19</sup>. In the Atherosclerosis Risk in Communities cohort study, all-cause mortality was 13.7% in those with OH compared to 4.2% in those without<sup>20</sup>.

The main goal in the treatment of OH is to alleviate the postural symptoms and improve functional capacity and quality of life rather than achieving a blood pressure target<sup>17,21,22</sup>.

The first step in OH treatment involves considering discontinuing or reducing dose of any medications that could potentially cause OH<sup>23</sup>. Non-pharmacological interventions are the first line of treatment for OH and pharmacological treatments are introduced only in severe cases of OH where non-pharmacological treatment is inadequate<sup>17,21,24-26</sup>. Although guidelines exist for managing OH, optimal non-pharmacological management is not well defined for the geriatric population. Indeed, the effectiveness of non-pharmacological treatment has been questioned<sup>27</sup>. There is a significant lack of research evidence in the fast growing population of older people with OH. Hence, we set out to fill this evidence gap as part of the SENATOR-ONTOP work package (Software ENgine for the assessment and Optimization of drug and non-drug Therapy in Older peRsons-Optimal Evidence-Based Non-drug Therapies in Older People)<sup>28</sup> with the view of development of evidence based recommendations for the non-pharmacological interventions for common geriatric conditions.

The aim was to assess the efficacy of non-pharmacological interventions in the treatment of OH in people aged ≥65 years.

## **Methods**

This review of systematic reviews was conducted according to the SENATOR-ONTOP protocol<sup>29</sup>. A literature search was undertaken on EMBASE, PubMed, the Cochrane Database of Systematic Reviews (CDSR), CINAHL, and PsycINFO from inception to 6<sup>th</sup> June 2018 to identify systematic reviews. Key search terms used included orthostatic hypotension, postural hypotension, orthostasis, orthostatic intolerance, orthostatic syncope and postural blood pressure. There was no language restriction, however authors planned to translate only papers published in Spanish and Italian languages. The search strategy was

restricted to 'human only' studies and publication type was limited to 'systematic review/reviews/meta-analysis'.

## **Study selection criteria**

We included systematic reviews and/or review articles that had evaluated any non-pharmacological intervention for treatment of OH, used at least one medical literature database for evidence searching, included at least one primary study, and evaluated at least one non-pharmacological intervention for the treatment of OH in older people.

We included any comparative study, either randomized or non-randomized clinical trials that investigated the effect of any non-pharmacological intervention in OH. Before-and-after studies (BAS) or repeated measure study design where patients acted as their own controls were included. We excluded observational studies or BAS with historical controls.

We included trials involving older people in which the mean age of participants was  $\geq 65$  years. For the purpose of this review, OH was defined as a drop in systolic BP  $\geq 20$  mmHg and/or a diastolic BP  $\geq 10$  mmHg determined by either active standing or passive tilt test<sup>30</sup>. Though our initial plan was to include only supine to standing OH, due to a lack of eligible studies in older people, we later included studies that evaluated the effect of non-pharmacological intervention in different positions, e.g. supine to seated or seated to standing.

## **Types of interventions**

Our review focused on trials of non-pharmacological interventions administered either alone or in combination with other non-pharmacological interventions. Comparator interventions included placebo, no treatment or sham procedure. We excluded control



interventions of active pharmacological and non-pharmacological treatments as this might not provide accurate efficacy data on the non-pharmacological interventions.

## **Types of outcome measures**

We conducted an online Delphi survey involving international experts from the field of geriatric medicine in order to select the most important outcomes measures for this review. Two outcome measures that were ranked as 'critical' by the Delphi panel for OH were included as the main outcomes for this review. These were:

- Outcome 1: Change in postural systolic BP drop (mmHg) from supine to standing
- Outcome 2: Orthostatic symptoms measured using any validated method.

## **Data collection and analysis**

Two reviewers independently screened the titles and abstracts, and selected potentially relevant review articles for full text review. From the included review articles, we identified eligible primary studies as per inclusion criteria and reference checking was performed to identify any additional eligible primary studies. After removing duplicates using reference manager software (Refworks®), two reviewers independently reviewed the full-text of the eligible primary studies for inclusion or exclusion. At each stage of screening and study selection, any disagreements were resolved by discussion and by consensus with the lead author wherever necessary. Two reviewers independently extracted data using a study specific data extraction form developed for this review.

## **Analysis**

The methodological quality of each SR was assessed using AMSTAR (A Measurement Tool to Assess Reviews) instrument<sup>31</sup>. The risk of bias for all the included primary studies was evaluated using the Cochrane collaboration's recommended risk of bias tool <sup>32</sup>. Risk of bias was rated by two reviewers independently, resolving disagreements by discussion and by consensus with the lead author when required.

The quality of evidence was assessed using the GRADE (Grading of Recommendations Assessments, Development and Evaluation) approach, which classifies evidence into four categories - high, moderate, low and very low<sup>33</sup>. PICO clinical questions were developed for each intervention and outcome, and authors completed grading assessment and summary of findings (SoF) using online software, GRADEpro<sup>®34</sup>.

The treatment effect size and heterogeneity were assessed as described in the SENATOR-ONTOP protocol<sup>29</sup>. Meta-analysis and forest plots were created where possible using the version 5.3 of RevMan<sup>®</sup> software when data from at least two primary studies could be combined. Each type of non-pharmacological intervention was evaluated separately and we chose the generic inverse variance statistical method. When there was not enough information reported on the paper for outcomes data, we contacted study authors by email. The size of the treatment effect was expressed as the mean difference between the intervention and control group. Narrative synthesis of the evidence was undertaken where meta-analysis was not possible.

## **Results**

A total of 2037 articles were retrieved after removing duplicates. We excluded 2029 non-relevant articles after screening titles and abstract, and eight systematic review articles were identified for full text review. We included six review articles after excluding two

review articles that did not meet inclusion criteria. Our search did not identify articles in any language other than English. The study selection process is illustrated in the PRISMA flow diagram (**Figure A1**).

Of the six review articles included, only one article was of high quality (AMSTAR score 8-11), three were of medium quality (scoring 4-7) and two were of low quality (scoring 0-3). The systematic review articles were heterogeneous, varied extensively in population and the intervention type. Three articles included pharmacological treatment for OH in addition to evaluating the non-pharmacological interventions.

From the six review articles, we identified 64 primary studies for abstract screening. Following the full-text review of 30 eligible primary studies, we included 11 primary studies in the review (**Figure A1**). Studies were conducted in Europe, USA, Australia, Japan and Israel between 1999 and 2017. Of the 11 included studies, six were observational studies with BAS design and five were RCTs (4 crossover design and one open RCT).

Study sample sizes ranged from 8 to 100 participants and took place in various settings including in-patient hospital wards, outpatient ambulatory departments, and community non-clinical areas (i.e. outside of hospital) and research laboratories. None of the studies reported sample size calculations. Studies included patients with various OH types (symptomatic, persistent OH, progressive OH) from various causes of OH. The definition and measurement of OH, and the outcomes reported varied considerably between studies.

Characteristics of the included studies are detailed in **Table 1**.

Our review identified seven different types of non-pharmacological interventions from 11 studies - lower limb compression, abdominal compression, combination therapy of lower limb and abdominal compression, sleeping with head-up (SHU), bolus water drinking, home

based resistance training (HBRT) and multi-component non-pharmacological intervention. Duration of interventions varied from one single time point assessment to a period of 8 weeks. Studies very rarely reported adverse events due to interventions. Based on non-pharmacological therapies that were identified in our review, we categorised the non-pharmacological interventions into two broad categories, compression therapy and others (Table 2).

Figure 1 shows the risk of bias assessment of individual studies. Risk of bias of the included studies was high in general, not only for the observational studies, but also for the RCTs mainly due to the type of study design. Risk of bias across studies (Figure A2) showed that nearly 75% of the studies had non-random sequence generation and lack of allocation concealment. Many of the studies included in this review used either BAS or crossover study design where patients acted as their own control, which limited the blinding of participants. Selective reporting and other types of bias were common in around 50% of the studies.

#### **Effectiveness of non-pharmacological interventions.**

Meta-analysis was performed for two non-pharmacological interventions, lower limb and abdominal compression bandage.

#### **Outcome 1: Change in postural systolic BP drop (mmHg) from supine to seating/standing**

Meta-analysis was undertaken on three studies comparing lower limb compression with no lower limb compression in 131 participants acting as their own controls (Figure 2). There was a significant improvement with lower limb compression (MD -9.83 mmHg, 95% CI -12.56, -7.11).

227 Three studies comparing abdominal compression with no abdominal compression on 50  
 228 participants acting as their own controls were suitable for meta-analyses (**Figure 3**). This  
 229 showed statistically significant benefit for abdominal compression therapy (MD -12.30  
 230 mmHg, 95% CI -18.20, -6.39).

231 One study<sup>35</sup> of graduated elastic compression hosiery (GECH) showed short term benefits in  
 232 improving symptoms of OH. Maximum mean (SD) SBP drop on standing with and without  
 233 GECH was 24.5 (7.9) and 52.2 (4.4) mmHg, ( $p < 0.005$ ) respectively. Orthostatic dizziness was  
 234 abolished in 7 out of 10 patients.

235 One study<sup>36</sup> investigated the combined treatment effect of lower limb and abdominal  
 236 compression bandage. Initial lower limb compression showed improvement in orthostatic  
 237 blood pressure on standing ( $10 \pm 5.56$  vs  $20 \pm 6.85$  mmHg), but addition of an abdominal  
 238 bandage showed no added benefit ( $10 \pm 6.17$  vs  $26 \pm 6.85$  mmHg).

239 One study<sup>37</sup> evaluated the physiological effects of SHU at 6-inches for 6 weeks but results  
 240 showed this was ineffective in improving blood pressure or symptoms.

241 One study<sup>38</sup> evaluated bolus water drinking where patients were asked to take 480 mL of  
 242 tap water in less than 5 minutes. Seating to Standing SBP 35 minutes before and after bolus  
 243 water drinking showed positive effect ( $83 \pm 20$  mmHg vs  $114 \pm 30$  mmHg,  $p < 0.01$ ) in  
 244 orthostatic blood pressure drop.

245 One study<sup>39</sup> investigated home-based resistance-training (HBRT), however the mean  
 246 reduction in SBP drop from supine to standing ( $36.8 \pm 13.4$  at week 1 vs  $43.8 \pm 3.4$  mmHg at  
 247 week 8,  $p > 0.05$ ) did not show any significant improvement in orthostatic blood pressure.

One study<sup>40</sup> evaluated a twelve component non-pharmacological intervention including: increased dietary salt (10–20 g daily); five glasses (250 mL/glass) of water per day; elevated head of bed (10–15 cm); thigh-high 30 mmHg compression stockings; frequent small meals (6 per day); coffee/tea in the morning; no alcohol use; avoiding exposure to hot ambient temperatures; avoiding strenuous early morning activities, sitting on the side of the bed for 30 seconds before rising in the morning; regular moderate intensity exercise (20 minutes three times a week) and avoiding prolonged standing. The multi-component intervention did not improve SBP on standing, though it quantitatively improved OH symptoms in 7 out of 17 participants.

## **Outcome 2: Efficacy of non-pharmacological interventions in improving OH symptoms.**

Our review identified two studies that had reported orthostatic symptoms using a validated questionnaire. One study<sup>36</sup> investigated the effect of lower limb compression stocking in reducing orthostatic symptoms using a 7-item Specific Symptom Scale Questionnaire for Orthostatic Intolerance (SSS-OI) questionnaire<sup>36</sup>. The baseline SSS-OI score of  $35.2 \pm 12.1$  decreased to  $22.5 \pm 11.3$  ( $p=0.01$ ) after 1 month therapy, indicating significant symptom improvement. Another study<sup>41</sup> compared no abdominal compression with a conventional elastic abdominal binder in 13 patients with neurogenic OH and measured severity of OH symptoms using Orthostatic Symptoms Scale (OSS)<sup>41</sup>. Median baseline OSS score improved from 5.0 points to -0.5 points five minutes after standing with conventional elastic abdominal binder.

## **Quality of Evidence GRADE quality assessment and summary of evidence**

GRADE quality assessment was very low for all the included studies primarily due to the poor study design, small sample size and short term follow up. **Appendix 3** shows the

271 Summary of Findings table's for lower limb and abdominal compression therapy for  
272 outcome 1.

## 273 **Discussion**

274 This is the first review of systematic reviews to summarize the evidence based  
275 recommendations for the non-pharmacological treatment of OH in an older population.  
276 Even though our meta-analysis showed statistically significant benefit favouring lower limb  
277 and abdominal compression therapy for management of OH in older people, the quality of  
278 included studies was very poor. There was substantial clinical heterogeneity among the  
279 three studies included for lower limb compression bandage. Two studies assessed the  
280 preventive effect from supine to seated OH and one study evaluated the treatment effect  
281 using a tilt table study. The lower limb compression pressure varied from 30 to 60mmHg  
282 with different pressures applied at different sites in the limbs. Furthermore, treatment  
283 duration varied from 5 to 20 minutes. In terms of population characteristics, two studies  
284 included OH patients with no specific cause or OH due to various acute conditions and one  
285 study included patients with OH due to acute decompensated heart failure.

286 Similar to lower limb compression, three studies that evaluated abdominal compression  
287 therapy showed large differences in the population included, variation in the abdominal  
288 compression pressure from 10 to 20 mmHg and in the definition and measurement of OH.  
289 Studies also failed to report information on the effect of OH after discontinuation of  
290 compression therapy. GRADE quality was therefore downgraded for both LL and abdominal  
291 compression therapy despite the meta-analysis showing positive effect size from the pooled  
292 estimate. Therefore, we cannot make strong recommendations for use of compression  
293 therapy in OH. In addition, caution should be applied in recommending these non-

pharmacological interventions because the lack of reporting of potential adverse effects is a concern. Our results and conclusions regarding the compression therapy are similar to those of Frith<sup>42</sup>. Interestingly, compression therapy has been recommended by two systematic reviews based on limited evidence but the authors recommended further studies due to lack of good quality evidence<sup>43,44</sup>. In addition, a recent study by Newton and Frith suggested disregarding compression therapy in the aging population<sup>45</sup>.

Based on the present review, there is no recommendation for any other types of non-pharmacological interventions in older people with OH as evidence was restricted to a single small and poor quality study for each. Although, combination treatment of sleeping head-up with fludrocortisone is frequently used for treating OH, this recommendation is mainly based on results from two studies which have included only younger people i.e. aged 64 years or younger, and small sample sizes<sup>46,47</sup>. Guidelines indicate the quality of evidence for recommending SHU for OH is low<sup>48</sup>.

Similar to the finding by Saedon et al<sup>5</sup>, we also observed from our review that OH definition, protocol for measuring orthostatic hypotension, and evaluation of postural symptoms varied greatly among studies. This is a most important factor to note as this might have potential impact on the detection of OH, and thereby efficacy of the interventions. In addition, some studies carried out OH measurements in the fasting state but many did not specify. Therefore, it is uncertain whether these studies evaluated for post-prandial hypotension, which is an important and different entity to be considered in the geriatric population.

## **Adverse events**



None of the included studies in our review reported adverse effects of non-pharmacological therapies except two studies which reported that increased fluid intake in OH people aggravated urinary incontinence and hyponatraemia resulting in confusion<sup>40</sup> and more ankle oedema in the intervention arm of the study evaluating SHU<sup>37</sup>.

## **Strengths and weaknesses of the review**

We used an international Delphi survey for selecting the most important outcome measures. We performed meta-analyses for lower limb and abdominal compression therapy after contacting authors which, to our knowledge, is the first review to synthesize evidence for the non-pharmacological treatment for OH in older people. Furthermore, the quality of the evidence was assessed systematically by applying the GRADE quality assessment tool. A limitation of our review is that it may have missed important trials that were published after the last systematic review was published. Our review was focused only on older people with OH. Therefore, it is possible that helpful interventions that have not been sufficiently tested in older people were missed. Almost all the studies excluded participants with recent changes in the prescribed therapy or reduced/discontinued vasoactive medications. However, the effects of medications on OH have not always been reported clearly, which is potentially important in multimorbid older people with polypharmacy. Usual measures of OH used in these studies may not be accurate to detect patients at risk<sup>49</sup>. Also, the recommendations from this review might not be applicable to specific populations of patients such as those with OH due to autonomic failure or spinal cord injury. Our review does not consider compliance issues. This may be relevant as Schoffer et al. reported that patients' compliance was lowest (46% in men versus 100% in woman) with OH for

338 compression stockings amongst the 12 non-pharmacological therapies that they had  
339 investigated<sup>40</sup>.

## 340 **Conclusions/implications**

341 Our review found that there is no strong evidence to recommend any of the non-  
342 pharmacological therapies for the management of OH. Nevertheless, we make a weak  
343 recommendation based on very low quality evidence for lower limb compression and  
344 abdominal compression bandage in treating OH in older people. The results of this review  
345 also emphasized the necessity to standardize the method of measuring OH.

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## 350 **Author contributions**

351 **SS:** Study design, screening, data extraction, data analysis, interpretation of data and  
352 drafting and finalising the manuscript for publication

353 **RLS:** Study concept and design, data analysis, interpretation of data, and critical review and  
354 approval of final version of the manuscript to be published

355 **PKM and KRM:** Study concept and design, supervision, and critical review and approval of  
356 final version of the manuscript to be published

357 **IB:** Study concept and design, data analysis, and critical review and approval of final version  
358 of the manuscript to be published

359 **DOM, AJC and AC:** Study concept and design, and critical review and approval of final  
360 version of the manuscript to be published

361 **SD:** Screening, data extraction and analysis

362 **Sponsor's Role:** Sponsor did not play any role in the study design, methods, data collection,  
363 analysis and preparation of paper.

364 **Conflict(s) of Interest/Disclosures(s)**

365 None.

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502 **Figure legend**

503 **Figure 1.** Risk of bias summary for individual study. Red (-) = high risk of bias, green (+) = low  
504 risk of bias and yellow (?) = unclear risk of bias.

505 **Figure 2.** Forest plot showing the meta-analysis of lower limb compression bandage. *Note:*  
506 *Patients acted as their controls, therefore the total sample size is 131.*

507 **Figure 3.** Forest plot showing the meta-analysis of abdominal compression binder *Note:*  
508 *Patients acted as their controls in all three studies, therefore the total sample size is 50.*

509 **Figure A1.** PRISMA flow diagram of study selection process. SCI: Spinal Cord Injury.

510 **Figure A2.** Risk of bias graph across all included studies.

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512

**Table 1.** Characteristics of primary studies.

Author	Study design	Setting & Population	Comorbidities & Type of OH	Definition of OH	Method of OH measurement	Further details on OH assessment	Intervention	Results
<b>Lower limb compression bandage</b>								
Gorelik et al 2004 <sup>50</sup>	Randomized crossover study (BAS)	In patient study; Passive Seating-induced OH; 61 patients; aged >65 years	Hospitalized for various acute conditions and remain bedridden for at least 36 hours.	Fall of $\geq 20$ mm Hg in SBP or $\geq 10$ mm Hg in DBP on sitting	Digital cuff BP measurement in supine and 1, 3 and 5min following passive seating (unbandaged & bandaged)	In the morning, prior to assuming sitting position. Excluded patients with previously diagnosed OH and hemodynamic instability	Lower limb compression bandages (30 mmHg pressure) applied from ankle to thighs before sitting	Change in mean SBP un-bandaged $17.8 \pm 16.8$ vs bandaged $5.3 \pm 12.0$ , ( $p < 0.001$ ); Symptoms significantly reduced in bandaged compared to un-bandaged.
Gorelik et al 2009 <sup>51</sup>	Non-randomized, uncontrolled BAS	In patient study; Seating-induced OH; 49 patients; Aged $\geq 60$ years	Acute Decompensated heart failure (chronic, NYHA grade II to IV), furosemide-treated patients	Fall of $\geq 20$ mm Hg in SBP and/or $\geq 10$ mm Hg in DBP on sitting from supine	Digital cuff BP measurement in supine and 1, 3 and 5min following passive seating (unbandaged & bandaged)	In the morning, while fasting and before drug administration; After clinical, hemodynamic stabilization & withdrawal of IV medications	Lower limb compression bandage from the ankle to thigh (40mm Hg pressure) before sitting	Mean change in SBP of un-bandaged $18.3 \pm 14.1$ vs bandaged $10.9 \pm 12.7$ , ( $p = 0.001$ ). OH Symptoms appeared in 22.4% of un-bandaged vs 12.2% of bandaged ( $p = 0.1$ ).
<b>Abdominal compression</b>								
Yamamoto et al 2006 <sup>52</sup>	Uncontrolled BAS	In patient study; 25 patients; Mean age:	Chronic hemodialysis with intractable	Improvement in mean SBP after HD with the	SBP at supine and 1min after active standing, measured with	Did not eat and did not administer antihypotensive medications	Abdominal compression with an inflatable abdominal band	Change in mean SBP after HD without band - $36.2 \pm 18.0$ vs with band $-19.4 \pm 21.2$ mm Hg,

		68.3 ± 10.9 years	post-dialytic OH (Drop in SBP ≥15 mm Hg upon standing and hypotensive symptoms soon after HD)	band ≥25mm Hg	and without band, following 15 rest after HD	during study; Excluded patients with hypervolemia and chronic hypotension	(air bag inflated to 20 mm Hg pressure)	(p<0.002)
Fanciulli et al 2016 <sup>53</sup>	Randomized cross over study	15 patients; Mean age: 69 years (range 66 to 75)	Parkinson's Disease with symptomatic OH	Not defined, calculated mean SBP and DBP changes 3min after head-tilt up and 3min after active standing.	Both tilt-table at 60° and active standing test, using continuous non-invasive BP monitoring (10min supine, 10min head-up tilt, 5min supine & 5min standing)	Assessed OH between 9am to 12pm, excluded patients with changes in medications 6 weeks preceding enrollment and other major neurological conditions	Elastic abdominal binder (20 ± 2 mm Hg pressure) versus Placebo binder (3 ± 2 mm Hg) on the abdominal wall)	Mean difference in SBP between abdominal binder versus placebo was +10 ± 10.2 mm Hg (P= 0.006)
Figuerola et al 2015 <sup>41</sup>	Randomized crossover trial	Autonomic Research laboratory; 13 patients; Median age: 72 years	Neurogenic OH with PD, diabetic neuropathy, MSA or other neurological condition associated with autonomic failure	supine to standing (within 5min of standing) drop of ≥30mmHg SBP and ≥15mmHg DBP	Supine to active standing via continuous beat-to-beat arterial BP using plethysmography	Withheld anticholinergic, α and β adrenergic agonist for at least 5 half-lives prior to the study, midodrine the night before evaluation, permitted Fludrocortisone doses ≤0.2mg/day	Abdominal compression with conventional elastic abdominal binder (10mmHg pressure for 2min) versus no abdominal binder, remained erect for 5min	Change in median SBP with (-50 mmHg; IQR, -33 to -70mmHg) vs without (-57mmHg; IQR -40 to -76 mmHg) abdominal compression

**Lower limb compression combined with abdominal compression**

Podoleanu et al 2006 <sup>36</sup>	Randomized crossover study	21 patients; Mean age: 70 ± 11 years	Symptomatic progressive OH, not mentioned any specific condition/cause of OH	Progressive decrease in BP with occurrence of symptoms during diagnostic tilt testing	Acute-tilt table test at 60° using noninvasive digital cuff SBP measurement in supine and standing 2 min and 10min and 20min head-up tilt or onset of OH symptoms	Not reported	Lower limb compression bandages (40 to 60 mmHg at ankles & 30 to 40 mmHg at hips) for 10min followed by abdominal compression (20 to 30 mmHg) for 10min vs Sham bandage (5mm Hg overall)	Change SBP after active vs sham Lower limb compression: 10±5.56 vs 20±6.85 mmHg and after adding abdominal compression: 10±6.17 vs 26±6.85 mmHg
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#### Lower limb compression hosiery

Henry et al 1999 <sup>35</sup>	Non-randomized BAS	Geriatric falls clinic; 10 patients; Mean age: 77.2 years; (range 62 to 89)	Persistent (reproducible) symptomatic OH with H/o falls	Sustained drop in SBP of >20 mm Hg (average SBP over the whole 3 min) from supine to standing	Continuous BP reading in 3min supine and 3min passive head up tilt to 90° using digital BP device	Studied each patient least 2 hours after breakfast or lunch	Graduated Elastic Compression Hosiery (GECH), 20–30 mmHg pressure at ankles	Maximum mean SBP without 52.2 (4.4) vs with GECH 24.5 (7.9) mmHg, (p <0.005). orthostatic dizziness was abolished in 7 out of 10 patients
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#### Sleeping-head-up (SHU)

Fan et al 2011 <sup>37</sup>	Open Randomized Controlled Trial	Community dwelling, 100patient; aged ≥ 60 years	OH from all cause	symptomatic OH according to consensus criteria	24hr ABPM & phasic beat-to-beat digital Photoplethysmography during 5min supine rest & at	Patients performed active stands between 9 and 11 hours; Increased water intake to at least 2 litres a day;	SHU at 6 inches versus no head elevation during sleep for 6 weeks	No significant difference in standing SBP, DBP or MAP and symptoms before or after the intervention between groups.
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2min active standing

Reduction or discontinuation of medications that lower BP at least a month prior to study

### Bolus water drinking

Shannon et al 2002 <sup>38</sup>	BAS	11 patients; Mean age 69.8 years (range 54 to 83)	Severe OH due to primary autonomic failure (Pure autonomic failure & MSA)	Severe OH, No OH criteria defined	Seating BP (every 5 min for 30min) and upright standing BP at 1min using automated brachial BP cuff	Discontinue vasoactive medications & fludrocortisone at least 5 half-lives prior to study, To consume diet containing 150 mmol of sodium and 70 mmol of potassium for at least 3 days before, and not to drink for at least 1.5 hours before testing, Assessed OH at least 2.5 hours after breakfast or lunch	480 mL of bolus water (tap) drinking at room temperature (20° C) in less than 5 minutes. Measured standing BP 35min after bolus water drinking	Standing SBP before and 35min after bolus water drinking was 83±20 vs 114±30 mmHg, (p<0.01); Tolerated standing time improved from 5±3min to 11±10min in 6patients
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### Home-based resistance-training

Zion et al 2003 <sup>39</sup>	Non-randomised, BAS	8 patients; Median age 73.5 years	No specific cause for OH mentioned	Decrease in SBP of >20 mm Hg or DBP of >10	Abbreviated title table test after 12-15min of supine rest,	Overnight fasting, Not to consume caffeinated products within 4	Various HBRT exercises using elastic resistance bands (5–8 min	Mean change in SBP at week 1 and 8 was
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(range 63 to 81)	mm Hg within 3min of standing	and head-up tilt to 60° for 20 min	hours of testing, No exercise performed 24 hours prior to testing, refrain from taking midodrine morning dose.	of a warm-up, 25 minutes of strengthening & 5 min of cool-down/stretching exercises, every other day (4day/week) for 8 weeks	36.8±13.4 vs 43.8±13.4 mmHg, not significant.
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**Multi-component non-pharmacological therapy**

Schoffer et al 2007 <sup>40</sup>	BAS	17 Clinic patients; mean age: 69±11 years	OH in patients with idiopathic Parkinson's Disease	Fall of ≥20 mm Hg in SBP and/or ≥10 mm Hg in DBP within 3min of standing	Bedside postural BP testing via automatic sphygmomanometry by a physician in supine and standing 1 and 3min	Sustained response to medications, held stable throughout study; Excluded patients with ACS and severe hypertension	12 different types of multi-component non-pharmacological intervention	Multi-component non-pharmacological therapy did not significantly alter the drop in SBP on standing. Quantitatively, 7 of 17 patients noted an improvement in OH symptoms.
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514 OH: Orthostatic hypotension; BAS: before-and-after study; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BP: Blood Pressure; NYHA: New York

515 Heart Association; HD: Haemodialysis; PD: Parkinson's Disease; MSA: Multiple System Atrophy; IQR: Inter Quartile Range; GECH: Graduated Elastic

516 Compression Hosiery; SHU: Sleeping with Head-Up; ABPM: Ambulatory Blood Pressure Monitor; MAP: Mean Arterial Pressure; HBRT: Home-based

517 resistance-training; ACS: Acute Coronary Syndrome.

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**Table 2.** GRADE Quality of evidence for the various non-pharmacological interventions.

<b>Intervention category</b>	<b>Intervention subtype</b>	<b>No. of studies</b>	<b>GRADE score</b>
Compression therapy	Lower limb compression bandage	3	Very low
	Abdominal compression	3	Very low
	Lower limb combined with abdominal compression	1	Very low
	Lower limb compression with graduated elastic compression hosiery	1	Very low
Others	Sleeping-head-up at 6 inches	1	Very low
	Bolus water drinking (480ml of tap water in <5minutes)	1	Very low
	Home-Based Resistance Training program	1	Very low
	Multi-component non-pharmacological therapy	1	Very low

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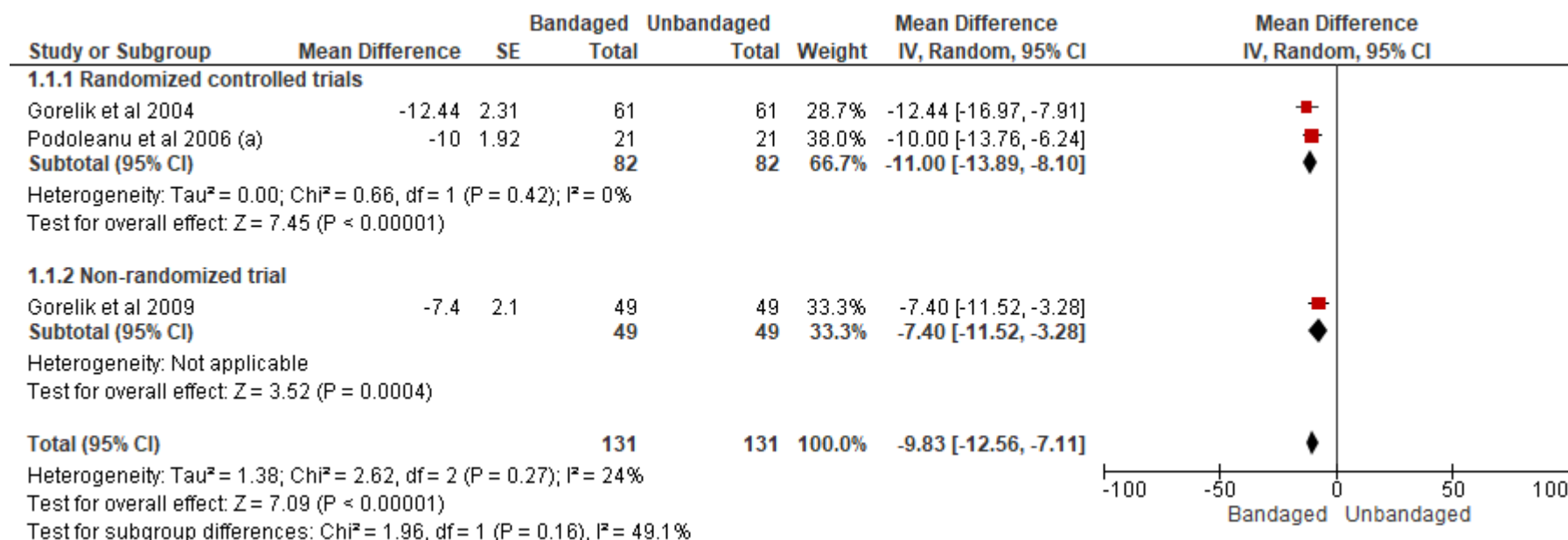
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## Figures

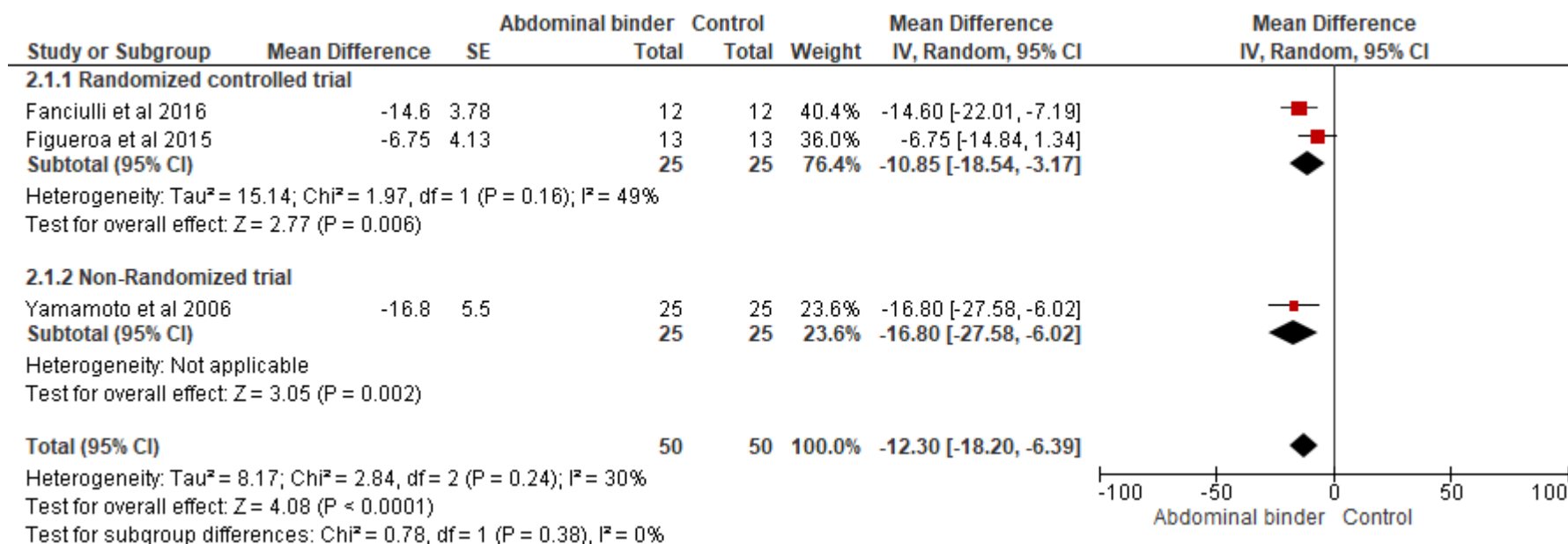
**Figure 1.** Risk of bias summary for individual studies. Red (-) = high risk of bias, green (+) = low risk of bias and yellow (?) = unclear risk of bias.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Fanciulli et al 2016	-	?	+	+	+	+	+
Fan et al 2011	+	-	-	?	-	-	+
Figueroa et al 2015	+	?	+	+	?	+	?
Gorelik et al 2004	?	?	?	?	+	-	-
Gorelik et al 2009	-	-	+	?	+	-	?
Henry et al 1999	-	-	+	-	+	+	+
Podoleanu et al 2006 (a)	+	-	+	+	?	-	-
Podoleanu et al 2006 (b)	-	-	-	-	?	+	-
Schoffer et al 2007	-	-	-	-	+	+	?
Shannon et al 2002	-	-	+	-	+	-	-
Yamamoto et al 2006	-	-	+	?	+	+	-
Zion et al 2003	-	-	+	+	+	-	-

534 **Figure 2.** Forest plot showing the meta-analysis of lower limb compression bandage. *Note: Patients acted as their controls, therefore the total*  
 535 *sample size is 131.*



540 **Figure 3.** Forest plot showing the meta-analysis of abdominal compression binder *Note: Patients acted as their controls in all three studies,*  
 541 *therefore the total sample size is 50.*



## **Appendices**

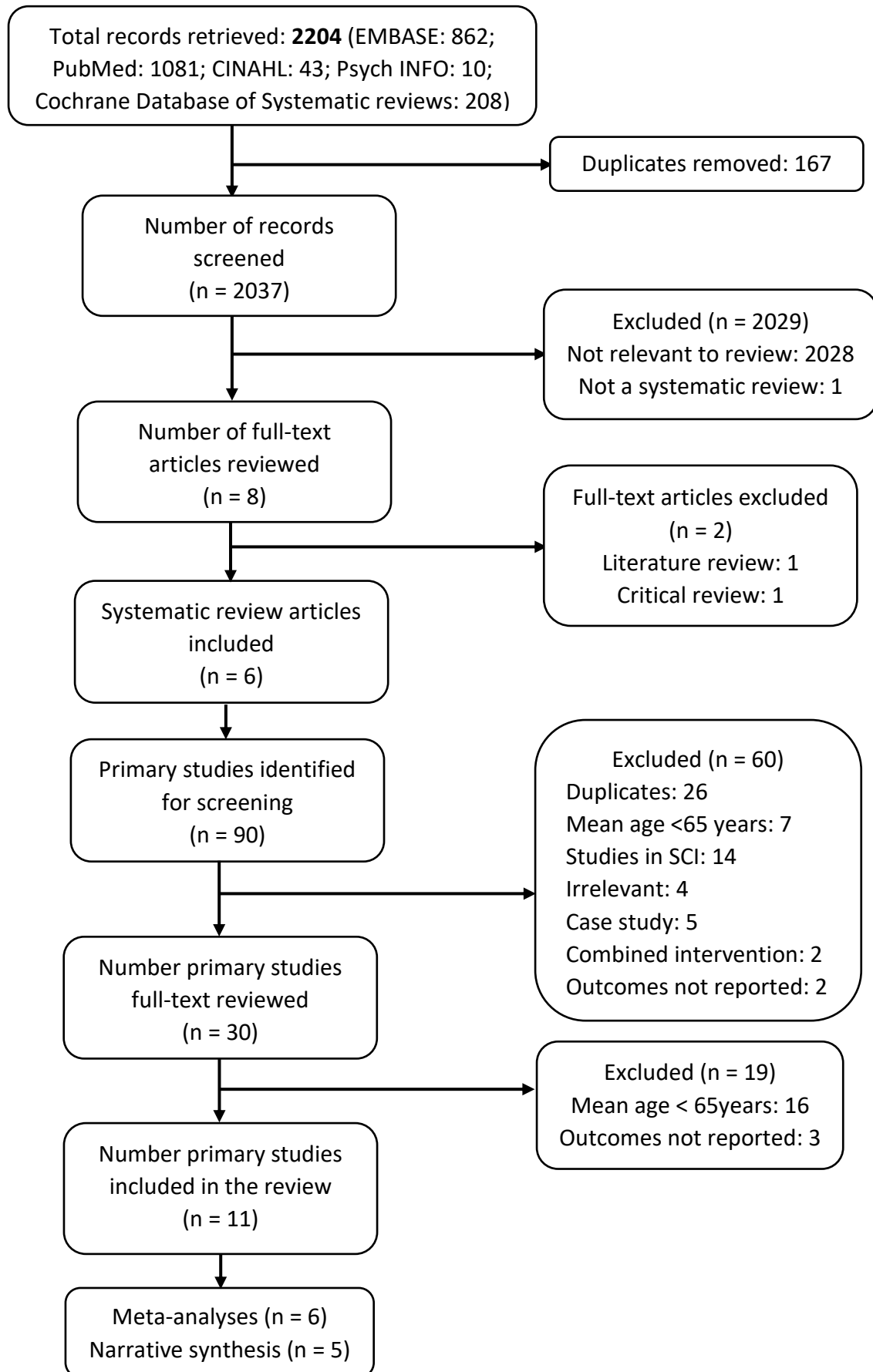
Appendix 1: PRISMA flow diagram

Appendix 2: Risk of bias across studies

Appendix 3: GRADE Summary of Findings tables for LL and abdominal compression bandage.

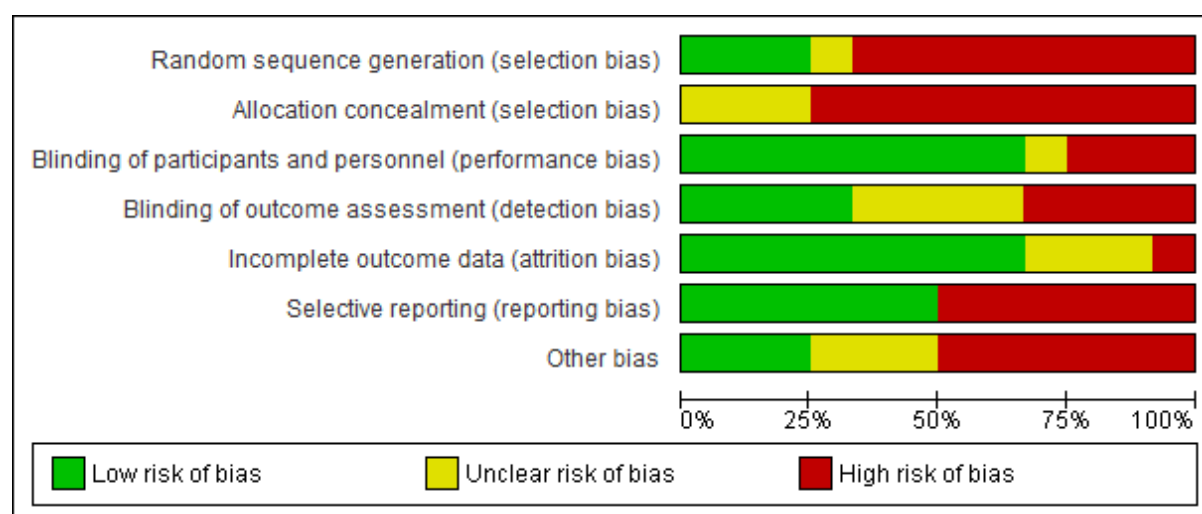
## Appendix 1: PRISMA flow diagram

**Figure A1.** PRISMA flow diagram of study selection process. SCI: Spinal Cord Injury.



## Appendix 2: Risk of bias across studies

**Figure A2.** Risk of bias graph across all included studies.



Red (-) = high risk of bias, green; (+) = low risk of bias and yellow; (?) = unclear risk of bias.

### Appendix 3: GRADE quality assessment for outcome 1: Change in postural SBP drop (mmHg) from supine to seated/standing

**Question1:** Lower limb (LL) compression bandage compared to no LL compression bandage for prevention and treatment of OH in older people

**Setting:** In-patient

**Bibliography:** Podoleanu et al 2006, Gorelik et al 2009 and Gorelik et al 2004

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lower limb (LL) compression bandage	no LL compression bandage	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials <sup>a</sup>	serious <sup>b</sup>	not serious	very serious <sup>c</sup>	serious <sup>d</sup>	all plausible residual confounding would reduce the demonstrated effect	131	131	-	MD <b>9.83 lower</b> (12.56 lower to 7.11 lower)	⊕○○○ VERY LOW	CRITICAL

**CI:** Confidence interval; **MD:** Mean difference

a. Two RCTs (cross-over and before-and-after study) and one non-RCT (before-and-after study)

b. >50% of studies with non-random sequence generation, lack of allocation concealment and selective outcome reporting

c. One study undertaken only in patients with acute decompensated heart failure. Two studies measured supine to sitting blood pressure change. Variation in the definition and measurement of OH.

d. Small sample size



15 **Question2:** Abdominal compression binder compared to control group for treatment of OH in older people

16 **Setting:** In-patient

17 **Bibliography:** Fanciulli et al 2016; Figueroa et al 2015 and Yamamoto et al 2006

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abdominal compression binder	control group	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>c</sup>	very serious <sup>d</sup>	all plausible residual confounding would reduce the demonstrated effect	50	50	-	MD <b>12.30 mmHg lower</b> (18.20 lower to 6.39 lower)	⊕○○○ VERY LOW	CRITICAL

18 **CI:** Confidence interval; **MD:** Mean difference

19 a. Two RCTs (cross over study) and one Non-RCT (before-and-after study)

20 b. Non-random sequence generation in two studies with unclear and high risk for lack of allocation concealment in all 3 studies

21 c. Included OH patients with certain specific medical condition (post-haemolytic OH and neurogenic OH). Methodological heterogeneity with differences in the definition and measurement of OH.

23 d. Small sample size of 50 patients, patients served as their own control in all three studies. Effect size with wider confidence interval

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